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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,614	02/06/2006	Stefan Golz	Le A 36 493	6701
35969 7590 03/31/2009 Barbara A. Shimei Director, Patents & Licensing Bayer HealthCare LLC - Pharmaceuticals 555 White Plains Road, Third Floor Tarrytown, NY 10591				
EXAMINER				
LONG, SCOTT				
ART UNIT		PAPER NUMBER		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/537,614

Applicant(s)

GOLZ ET AL.

Examiner

SCOTT LONG

Art Unit

1633

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2/14/2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6 and 9-16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6 and 9-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/14/2009 has been entered.

Claim Status

Claims 1-4, 6 and 9-16 are pending. Claims 5 and 7-8 are cancelled. Claims 1, 2, and 4 are amended. Claims 13-16 are newly submitted. Claims 1-4, 6 and 9-16 are under current examination.

Priority

This application claims benefit as a 371 of PCT/EP03/13281 (filed 11/26/2003). The application also claims benefit from the foreign (German) patent application 10257354.9 (filed 12/9/2002). The instant application has been granted the benefit date, 9 December 2002, from the German application 10257354.9.

RESPONSE TO ARGUMENTS

Claim Objections

The objections to claims 1(d) and 7 are withdrawn in response to the applicant's claim amendments

35 USC § 112, first paragraph (written description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6 and 9-12 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons of record and the comments below. In addition to maintaining the pending rejections, the examiner has extended the written description rejection to also reject claims 13 (formerly claim 7) and 16 (formerly claim 8) and new claims 14-15. Therefore, claims 1-4, 6, and 9-16 are rejected under 35 USC § 112, first paragraph (written description).

The applicant's arguments have been fully considered but are unpersuasive.

The applicant makes 4 arguments regarding the written description rejections:

(1) Because the art knows the structure and function of each and every amino acid in GFP, therefore the applicant is in possession of the claimed genus of nucleic acids sharing homology to SEQ ID NO:1 and to nucleic acids encoding proteins sharing homology to SEQ ID NO: 2. While many variants of GFP are known in the art, the applicant claims that their nucleic acid sequence SEQ ID NO:1 and amino acid

sequence SEQ ID NO:2 are novel and have excitation and emission spectra which differs from other known GFPs. Since this distinct characteristic is critical to the claimed invention and the specification does not describe which particular amino acids are essential for the unique excitation and emission spectra, the examiner concludes that a skilled artisan would not believe the applicant was in possession of a genus of molecules 95% homologous to the claimed GFP. Therefore, the examiner finds the arguments on pages 7-13 of Remarks (filed 2/14/2009) unpersuasive. Therefore, claims 1, 2, 3, 6, 13 (formerly claim 7) and 16 (formerly claims 8) remain rejected under 35 USC 112, 1st paragraph (written description).

(2) The applicant argues "written description for a genus of antibodies is found so long as the specification provides a well-defined antigen since antibody preparation and technology is routine in the art" (Remarks, page 13). To support his position, the applicant refers to Example 16 of the Written Description Guidelines. The specification's only mention of antibodies directed to the whole GFP or portions of the GFP claimed by the applicants is "The invention related to peptides, having more than 5 contiguous amino acids which are recognized immunologically by antibodies to the fluorescent protein according to the invention" (page 13, lines 10-12). The examiner notes that this is not an explicit recitation of antibodies immunogenic against the fluorescent proteins of the instant invention; rather it is a recitation of peptides which could be recognized by a variety of commercially available antibodies. This is especially true because the exact epitopes are not described and many antibodies are available which recognize other GFPs. As mentioned in the previous action, the

specification contains no specific claim of an antibody (in originally filed claim set) or description of an embodiment of an antibody immunogenic against the claimed fluorescent protein. For that reason, the examiner concluded there is no written description. The examiner did not explicitly identify claim 9 as new matter, but it is not supported by the teachings of specification. However, if claim 14 is admitted, it will be rejected under New Matter. Therefore, claim 9 remains rejected under 35 USC 112, 1st paragraph (WD).

(3) The applicant argues that claim 10 is not new matter, because while the exact steps of amended claim 10 were not taught in the instant specification, claim 10 recites steps which are "merely conventional steps well-known in the art for using any fluorescent protein as a marker gene or reporter gene" (Remarks, page 15). The examiner enjoyed reading this argument and hopes this becomes case law, since it would be very helpful in obviousness art rejections. Unfortunately, the examiner asserts that actual support in the specification is required in order for a method containing specific steps can be considered for allowance. Since these "conventional steps" are not recited in the specification, the examiner remains convinced that there is no support in the specification and it is new matter. Therefore, the claim 10 remains rejected under New Matter.

(4) The applicant argues that because they have overcome the written description rejection for claim 1, that they have also overcome the WD rejection for dependent claims 4, 11, and 12. The examiner has maintained the rejection of claim 1,

so he likewise maintains the rejection of claims 4, 11 and 12 under 35 USC 112, 1st (WD).

Therefore, the examiner hereby maintains the rejection of claims 1-4, 6 and 9-16 under 35 USC § 112, first paragraph (written description).

The examiner reiterates and elaborates the pending rejection:

Claims 1-4, 6 and 9-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The pending claims are directed to several inventions:

Claims 1-4, 11-12 and 15 are directed to a genus of isolated nucleic acids, vector comprising said nucleic acids, and host cell comprising said vector. Claims 13 and 16 are directed to a method of producing a fluorescent protein comprising a host cells containing said isolated nucleic acids. Claim 10 is directed to a method of detecting a fusion gene comprising said isolated nucleic acids. Therefore, claims 1-4, 10-13 and 15-16 all require the full breadth of the claimed nucleic acids.

Claim 6 are directed to a genus of isolated proteins encoded by the claimed nucleic acids.

Claims 9 and 14 are directed to isolated antibodies.

The instant claims encompass a genus of nucleic acids having at least 90% to identity to SEQ ID NO:1-2 and having anti-apoptotic activity of at least 70%, 80%, 90%

and 95% inhibition. Under the new Written Description Guidelines (March 25, 2008, Revision 1) the examiner is directed to determine whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing. The following considerations are critical to this determination:

a. Actual Reduction to Practice. In the instant case, the specification has reduced to practice a single embodiment of a polypeptide (SEQ ID NO:2) which has fluorescence activity having an excitation peak of about 475 nm and an emission peak of about 493 nm. The specification also provides the polynucleotide (SEQ ID NO:1) which encodes SEQ ID NO:2. The specification does not provide any embodiments of the claimed genera of polynucleotides and polypeptides except SEQ ID NO:1 and SEQ ID NO:2. The specification has not reduced to practice any antibodies which are immunogenic against SEQ ID NO:2.

b. Disclosure of structure. The applicant has provided sequence listings of SEQ ID NO:1 (DNA) and SEQ ID NO:2 (RNA). Additionally, with the help of a computer, a skilled artisan could identify all nucleic acids which are at least 95% identical to the full length sequence of SEQ ID NO:1. However, neither the specification nor the art indicate a relationship between the structure of the claimed genus of nucleic acids and the recited fluorescence activity having an excitation peak of about 475 nm and an emission peak of about 493 nm. In particular, there is no indication in the art or specification as to the effect of varying up to 5% of the nucleic acids of the claimed genus of isolated polynucleotides on the fluorescence function of the encoded polypeptides that are not 100% identical to SEQ ID NO:2. The specification and

originally filed claims do not recite "an isolated antibody which specifically binds any of the genus of claimed fluorescent proteins;" claims to antibodies are new matter.

With respect to claims limiting a polynucleotide by hybridization conditions, even under relatively high stringent conditions, the claimed nucleotide sequence could hybridize to a genus of polynucleotides that are similar, but not identical to the recited polynucleotides. The limitation by hybridization is obviously generic to a considerable number of nucleotides varying in the length of the nucleic acids, the degree of homologies among the sequences, and the biological activities of the encoded polypeptides, which may or may not have identical fluorescence characteristics. This genus also embraces sub-sequences that are unknown and include unsequenced polynucleotides, whose function is yet to be determined. The nucleic acids might also encompass very large nucleic acids that hybridize under highly stringent conditions only over a short range near one end of both sequences. In this case, there would be a very low level of homology between the two sequences, despite high stringency hybridization. Furthermore, there are no working examples of nucleic acids that have been isolated through the stringent hybridization method.

c. Sufficient relevant identifying characteristics. As mentioned in "b" above, the complete sequence of SEQ ID NO:1-2 are provided. Furthermore, the functional characteristics of these sequences have been demonstrated in Example 5 (Spec., page 19). The polypeptide sequence (SEQ ID NO:2) encoded by polynucleotide sequence (SEQ ID NO:1) demonstrates fluorescence activity having an excitation peak of about 475 nm and an emission peak of about 493 nm. In Example 5, it seems that a skilled

artisan would be clearly able to test a genus of polypeptides having at least 95% identity to SEQ ID NO:2. However, the new written description guidelines indicate in Examples 10 and 11A that without disclosure about which nucleotides can vary from SEQ ID NO:1 (and its corresponding polypeptide SEQ ID NO: 2) and still retain the claimed activity, the examiner should conclude that the applicant was not in possession of the claimed genus of isolated nucleic acids based on disclosure of the single species of SEQ ID NO:1 (and its corresponding polypeptide SEQ ID NO: 2).

d. The method of making the claimed inventions is not well established. Isolating a nucleic acid which encodes a fluorescent protein by a method of hybridizing DNA, is not well established, because it is not possible to know if nucleic acids encoding non-fluorescent proteins would be isolated by such a method. Making a polypeptide having at least 95% homology to SEQ ID NO:2 with fluorescence having an excitation peak of about 475 nm and an emission peak of about 493 nm is not well established. The process of making antibodies is generally well established.

e. The level of skill in the art is high, with most artisans having education at the PhD or MD level.

f. The predictability in the art for some of the claimed inventions are predictable, while others are not very predictable to a skilled artisan. Based on the state of the art and the disclosure of the instant specification, it would be unpredictable to which nucleotides of SEQ ID NO:1 can be varied and still produce a polypeptide having at least 95% homology to SEQ ID NO:2 with fluorescence having an excitation peak of about 475 nm and an emission peak of about 493 nm. The structure/function

relationship between the sequence of SEQ ID NO:2 and the recited excitation/emission spectra are not taught by the art or the specification. Therefore, no predication can be made.

Therefore, the examiner concludes that there is insufficient written description of the instantly claimed genus.

The literal sequences SEQ ID NO:1 and 2 are free of the art.

Therefore, the examiner hereby maintains the rejection of claims 1-4, 6 and 9-16 under 35 USC 112, 1st paragraph (written description) for the reasons of record and the comments above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 6 remains rejected under 35 USC 102(b) as anticipated by Levine et al (Compar. Biochem. Physiol. B, 1982. 72; 1:77-86).

Applicant's arguments (Remarks, pages 17-23) and claim amendments filed 14 February 2009 have been fully considered but are unpersuasive.

The applicant argues that the GFP taught by Levine is not the same as the fluorescent protein of instantly claimed SEQ ID NO:2. Specifically, the applicant states,

"LEVINE did not provide a purified green fluorescent [protein]...did not provide or determine the amino acid sequence of its green fluorescent protein, and did not provide the corresponding nucleic acid sequence. (Remarks, page 18). The examiner agrees with the applicant's assertion that Levine et al. do not provide a nucleic acid sequence or amino acid sequence for the Green Fluorescent protein described in their reference. However, claim 6 recites "an isolated protein encoded by the nucleic acid molecule of claim 1." Although the applicant has defined their GFP using SEQ ID NOs, Levine isolated their GFP using conventional protein purification methods in 1982, rather than to more recent molecular biological methods commonly used today. Nevertheless, if the Levine protein is the same protein as that of claim 6, as asserted by the examiner, then Levine would inherently satisfy the sequence related claim language. In addition, Levine et al. teach "isolation and characterization of...a spectrally unique green-fluorescent protein" (title). Therefore, the examiner finds this argument unpersuasive.

The applicant attempts to prove that the Levine GFP and the instantly claimed GFP are different proteins. While the applicant acknowledges that both the applicant and Levine isolated their green fluorescent proteins from the same organism, the applicant contends that they are not the same protein. The applicant proposes that they might be different fluorescent proteins within the same organism. The applicant provides several facts to support his position.

The applicant cites the molecular weight of the Levine GFP as 57,000 +/- 4% grams/mol (as determined by gel filtration), while indicating that the SEQ ID NO:2 GFP is 26,385.0 grams/mole (as determined by x-ray crystallography). Levine discusses the

variations between their methods and those of other laboratories when measuring the apparent molecular weights of other GFPs in the same paragraph as that revealing their estimation of P-GFP to be 57,000 +/- 4% grams/mol. The implication is that their measurement may not be completely accurate. In fact, Levine et al. suggest that the apparent molecular weights may vary by 20 to 50% (page 80, col.1, 2nd parag to col.2, top). Therefore, the examiner does not conclude that the discrepancy between the molecular weights presented by Levine and the applicant is a persuasive argument.

The applicant provides a comparison of the excitation and emission spectra for both SEQ ID NO:2 and P-GFP (Levine) in Schematic 1 (Remarks, page 20). The applicant makes several conclusions based on the data shown in Schematic 1. The applicant concludes that the "shoulder-peak at around 425 nm" is a significant difference between the two proteins. The examiner reminds the applicant that there is a control in the application's Figure 4 with a peak at about 425 nm. If this "background" were subtracted, the "shoulder-peak" would be eliminated, thereby smoothing the applicant's curve to match that of the Levine GFP. In addition, the applicant points out the apparent difference between the double peak of excitation (shown in Fig.4 of the specification) and the single peak of excitation shown in Levine. The double peak in the application's GFP excitation profile is not a characteristic of a single fluorescent protein. In fact, since it is clear that there are contaminating fluorescent proteins, excited at about 435 nm, the examiner concludes that there are either two different proteins having close, but not identical excitation wavelengths or two variant forms of the same protein. Therefore, the examiner believes this difference in profiles is not a

convincing argument that SEQ ID NO:2 and P-GFP are different proteins. Regarding the estimation of excitation and emission maximums (discussed on Remark, page 21), the examiner reminds the applicant that the examiner used his eyeballs to estimate the excitation and emission maximum of SEQ ID NO:2, since the instant application does not specifically state this data. Therefore the very small difference between the spectra for the GFP of Levine and the GFP of SEQ ID NO:2 can be attributed to the examiner's poor eyesight and the resolution of the Figures. In elaborating on the difference between the maximum peaks of P-GFP and that of SEQ ID NO:2, the applicant also bases part of his analysis on the eyeball estimation of the examiner. Therefore, the examiner finds the applicant's arguments unpersuasive.

Finally, the applicant reiterates his assertion that Levine does not teach an isolated GFP, its amino acid and nucleic acid sequences. As stated above, the instant claim is directed to an isolated protein. The examiner believes that Levine inherently teaches the isolated protein of SEQ ID NO:2, for the reasons of record and the comments above. Therefore, the examiner hereby maintains the rejection of claim 6 as anticipated by Levine.

In conclusion, the examiner hereby maintains rejection of claim 6 under 35 U.S.C. 102(b) as being anticipated by Levine et al (Compar. Biochem. Physiol. B, 1982. 72;1:77-86).

The examiner reiterates the pending rejection:

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Levine et al (Compar. Biochem. Physiol. B, 1982. 72;1:77-86).

Claim 6 is directed to an isolated protein which is encoded by the nucleotide sequence of claim 1. Levine et al. teach a green fluorescent protein (phialidin, also known as clytin) isolated from *Phialidium gregarium*. This is the same protein taught by the instant specification as coming from the same organism with the alternate name, *Clytia gregaria*.

Accordingly, Levine et al. anticipated the instant claims.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Fraile-Ramos et al. (Molecular Biology of the Cell, June 2001; 12: 1737-1749).

Claim 14 is directed to an isolated antibody which specifically binds to the fluorescent protein of SEQ ID NO:2.

Fraile-Ramos et al. teach rabbit antibody against GFP. The instant specification describes the amino acid sequence of SEQ ID NO:2 as a Green Fluorescent Protein which has a 44% identity to the *Aequoria* GFP. Absent evidence to the contrary, the antibody of Fraile-Ramos et al. would bind epitopes of instant SEQ ID NO:2.

Therefore, Fraile-Ramos et al. anticipated the instant claim.

Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Tsien et al. (US-5,777,079, published Jul. 7, 1998).

Claim 15 is directed to an isolated nucleic acid molecules selected from the group consisting of:

- a) a nucleic acid molecule encoding a polypeptide having the amino acid sequence of SEQ ID NO:2;
- b) a nucleic acid molecule comprising the sequence of SEQ ID NO:1;
- c) a nucleic acid molecule which encodes a fluorescent protein having an excitation peak of about 475 nm and an emission peak of about 493 nm and whose complementary strand hybridizes under stringent conditions with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1; and
- d) a nucleic acid molecule comprising a sequence which is at least 95% homologous to SEQ ID NO: 1 and which encodes a fluorescent protein having an excitation peak of about 475 nm and an emission peak of about 493 nm.

Tsien et al. teach modifications of green fluorescent protein having markedly different excitation and emission spectra from wild type GFP (abstract). Furthermore, Tsien et al. teach a mutant GFP which has an excitation peak of about 475 nm and an emission peak of about 493 nm (See Fig.3a and Fig.3b). Tsien et al. teach the nucleic acid sequence which encodes the mutant GFP. Furthermore, the complementary strand of the Tsien nucleic acid would hybridize under stringent conditions with a nucleic

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acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1.

Therefore, Tsien et al. anticipated the instant claim.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Weitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner
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